

IN THE SPECIFICATION

Please amend the paragraph beginning at page 4, line 3, as follows:

Calcium channels comprise low-threshold channels that are activated by weak depolarizations, and high-threshold channels that are activated by strong depolarizations. The high-threshold channels represent a heteromultimeric complex  $\alpha_1\alpha_2\delta\beta$  and  $\gamma$ , in which the membrane-bound  $\alpha_1$  subunit, constituting the channel per se, is associated with an intracellular regulatory  $\beta$  subunit (or  $\text{Ca}_v\beta$ ) via its interaction domain (AID domain motif: **QQ-E- -L-GY- -WI---E** (SEQ ID NO: 12) (one-letter code: - representing any amino acid; Pragnell et al., Nature, 1994, 368, 67-70; figure 1) in which residues Y392, W395 and I396 are essential for the ~~biding~~ binding of the  $\beta$  subunit (De Waard et al., FEBS, 1996, 380, 272-276). The regulatory  $\beta$  subunit binds to the AID domain by its BID domain (beta interaction domain; De Waard et al., J. Biol. Chem., 1995, 270, 12056-12064), which is included in a GK-like domain (Hanlon et al., FEBS, 1999, 445, 366-370).

Please amend the paragraph beginning at page 4, line 33, as follows:

In the central nervous system, the N- and P/Q-type high-threshold calcium channels are directly involved in the triggering of synaptic function; the opening thereof under the effect of an action potential induces calcium entry into the presynaptic terminal. This signal triggers the secretion of neuromediators such as glutamate into the synaptic cleft, and thus the propagation of the nervous influx in the postsynaptic dendrite. N and P/Q channels are regulated by trimeric G-protein-coupled receptors (GPCRs) such as class III metabotropic glutamate receptors (for review: El Far and Betz, mentioned above) or noradrenergic, muscarinic, GABAergic (GABA: 5- $\gamma$ -aminobutyric acid), serotonergic or dopaminergic receptors, and opiate receptors (for review: Hille, Trends NeuroSci., 1994, 17, 531-536). It has been shown that the  $G\beta\gamma$  subcomplex is directly responsible for inhibition of the activity

of P/Q channels that results from direct binding of  $G\beta\gamma$  to the intracytoplasmic loop connecting membrane domains I and II (loop I-II) of the  $\alpha_1$  subunit (De Waard et al., Nature, 1997, 385, 446-450). As a result, this loop has several sites of interaction with  $G\beta\gamma$ , that overlap with the  $Ca_v\beta$  regulatory subunit-binding domain (AID domain; figure 1) a consensus motif **QQ- -R-L-GY** (SEQ ID NO: 11) of which, included in the AID domain, is essential for the binding of  $G\beta\gamma$  (figure 1; De Waard et al., Nature 1997, 385, 446-450; Zamponi et al., Nature 1997, 385, 442-446). Furthermore, the  $Ca_v\beta$  regulatory subunit appears to oppose the functional effect of G proteins (Bourinet et al., P.N.A.S., 1996, 93, 1486-1491). Thus, it would appear that this antagonism involves physical competition between the  $Ca_v\beta$  subunit and the  $G\beta\gamma$  protein at the AID region of the I-II loop (Dolphin et al., J. Physiol., 1998, 506, 3-11).

Please amend the paragraph beginning at page 22, line 31, as follows:

-figure 1 illustrates the overlap, in the I-II loop of the  $Ca_v\alpha_{2.1}$  subunit, of the domains for binding to the  $\beta$  subunit (AID domain) and to the  $G\beta\gamma$  complex (**QQIERELNGY- -WIKAE**) (SEQ ID NO: 12). The AID domain is represented by a black box (positions 383 to 400). The binding sites for the  $G\beta$  ( $G\beta\gamma$ ) subunit are represented by the hatched boxes; the site in the central position (**QQ- -R-L-GY**) (SEQ ID NO: 11) that is essential for the binding of the  $G\beta$  ( $G\beta\gamma$ ) subunit is included in the AID domain,

Please delete the original Sequence Listing.

Page 41 (Abstract), after the last line, beginning on a new page, please insert the attached substitute Sequence Listing.